Alterations in Serum Protein Levels in Acute Human Poliomyelitis: Rationale for Therapy

JACK SHELDON CHUDNOFF, M.D., *Los Angeles*

SUMMARY

Serial determinations of serum protein levels in acute human poliomyelitis revealed a progressive drop of the serum albumin level which bore close relationship to the amount of clinical paralysis. This loss of serum albumin began about the third day after onset of clinical symptoms and progressed to the tenth day or longer. The more severe the clinical involvement, the less was the tendency to spontaneous correction of the albumin deficiency. Declining serum albumin levels were concomitant with progressively rising serum globulin values.

When pooled irradiated human blood plasma was administered, the depleted serum albumin levels were stabilized or made to approach normal, depending upon the severity of clinical involvement. It is felt that the administration of blood plasma resulted in definite clinical benefit with regard to the severity, extent, and duration of paralysis.

SPORADIC reports in medical literature have attributed beneficial results to the administration of whole blood serum or plasma[3, 4, 5] in acute human poliomyelitis. Other reports have stated that no apparent benefit results from administering large amounts of gamma globulin,[1] in spite of experimental evidence that strains from the three recognized types of poliomyelitis virus are agglutinated experimentally very readily by gamma globulin derived from pooled human plasma.[2] No specific rationale has been advanced to justify therapy with blood plasma. Although use of plasma was on an empiric basis, the results in a few reported instances were described as dramatic. For that reason and because of other studies soon to be reported, systematic investigations of the blood electrolytes and serum protein levels in acute cases of human poliomyelitis were made during the epidemic of 1948 which occurred in Los Angeles County. During the epidemic, 3,165 cases were reported and 3,094 of the patients were admitted to the Los Angeles County General Hospital. The impact of such a case load of this crippling disease provided impetus to reexplore old therapeutic possibilities and to search for new.

Pilot observations of the serum protein levels in a group of 40 consecutive patients, all severely ill and all confined to respirators, revealed unexpected and startling alterations from normal. During the time these striking protein changes became apparent in the laboratory, gross peripheral edema also was evident in many of these patients. There was no apparent reason for the appearance of the edema. The period during which nutrition had been withheld was too brief for edema to have resulted, and the volume of parenteral fluids was insufficient to have contributed to edema. Obviously, further investigation into the entire subject of serum protein levels, especially albumin fractions, was imperative.

The correlation between low serum albumin and peripheral edema has long been established and accepted in cirrhosis of the liver, nephrosis, and other clinical diseases. A question that arises, then, is: If peripheral edema occurs — and peripheral edema was present in many of the patients observed — is it not feasible for interstitial edema to occur within the central nervous system and contribute to the paralysis? It has been observed frequently in this disease that the onset of paralysis occurs suddenly and extensively; also that its disappearance may follow the same variable course without adequate explanation: The nerves do not function but could not have been destroyed.

In order to explore the patterns of serum protein changes, it was decided to determine serum protein levels with albumin-globulin fractions in cases of graded severity. For this purpose, all cases in this study were empirically classified into three categories:

I. *Mild*—Cases of non-paralytic poliomyelitis, or cases in which there was paresis or paralysis totaling less than one-third of the body musculature. No cases of bulbar involvement were included.

II. *Moderate*—Cases in which there was paresis or paralysis of more than one-third of the total body musculature. Bulbar involvement was not excluded if the use of a respirator was not required.

III. *Severe*—Cases in which there was paresis or paralysis of more than one-third of the body musculature. Patients in this classification all had respiratory muscle or bulbar involvement, had had tracheotomy, and were in respirators.

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No equivocal cases were accepted for this study. It was not necessary to include borderline or transitional cases which could not be fitted into the three categories.

TABLE 1.—*Clinical Severity of Cases Studied: 75 Cases*

	Mild	Moderate	Severe
47 cases (Controls—conventional treatment only)	25	13	9
28 cases (Treated—conventional treatment plus plasma)	4	9	15

In each case studied serum protein levels and albumin-globulin fractions were determined daily for five days from the date of admission to the hospital. The day of admission to the hospital invariably was the day on which the case was accepted in this study. Following these initial determinations, levels were determined every second day for an additional five determinations; and if the patient remained in the hospital, levels were determined every third day thereafter. For those patients who were to be treated, levels were determined daily until the day of treatment, and on each treatment day the levels were determined before blood plasma was administered. At the termination of plasma treatment, invariably five consecutive days, levels were determined as before, every two days for five determinations, and every three days thereafter until the patient was discharged from the hospital. The plasma used for treatment in this study was pooled, irradiated human blood plasma, given in a dosage of 5 cc. per pound of body weight daily, for a minimum consecutive period of five days. With few exceptions, no more than 1,000 cc. of plasma was given to a patient on any single day.

It should be stated that all patients observed during this epidemic were given routine care and treatment. No specific measures were used either in diagnosis or treatment that would differ materially from the routine care given elsewhere to patients with acute poliomyelitis. Upon institution of this study, consecutive cases were accepted into the series, classified, and the patients observed closely in the manner described. In alternate cases, with few exceptions, in addition to the usual measures employed at this hospital, pooled, irradiated human plasma was given intravenously in the manner related. For purposes of description in this study, the cases in which plasma was given are considered "Treated" cases, as contrasted to the alternate paired cases of comparative severity in which plasma was not given and which are regarded as "Controls." "Treatment," as here used, means administration of plasma according to the previously stated schedule.

All laboratory determinations were performed in a research laboratory organized specifically for this project. Blood samples in which hemolysis was noted were discarded and new samples obtained. The serum proteins were separated by Howe's sodium sulfate method[6] and measured by the biuret method of Kingsley.[7] By this method the alpha globulin fraction is thrown down with the albumin. The computed error by which the albumin fractions are thus increased over true values ranges from 20 per cent to 35 per cent, or from 0.75 gm. to 1.25 gm. per 100 cc. It was technically not feasible to correct the values for this error; the albumin values in these protocols are therefore significantly above true value, especially since in this disease the globulin is shown to be elevated.

Almost without exception, about the third day of clinical illness, regardless of the severity of involvement, there was a progressive decline in the serum albumin in direct proportion to the severity of the paralysis. This decline, which began about the third day, tended to reach its greatest subnormal value by the tenth day. Subsequent clinical relapses in severe cases were again mirrored in a decline in albumin levels from the previous level. At the same time that albumin levels declined, the serum globulin values rose in direct proportion to the severity of the clinical involvement and continued to rise far into convalescence.

In the cases of mild involvement, the serum albumin levels tended to return to normal spontaneously, a trend evident by the tenth day. In cases of moderate involvement, the drop reached its maximum by the tenth day and showed a tendency gradually to return to normal, but the level did not reach a normal for some time; in fact, at the end of three to four weeks of observation in the cases that were followed for that length of time, levels had not yet attained normal. In the severe cases, albumin depression was most severe by the tenth day of illness and showed little or no tendency to revert toward normal. In some severe cases followed for periods of 60 to 90 days, serum albumin levels still were low at the end of that time. In the event of clinical relapse, or extension of paralysis, the partial stabilization at a subnormal level that had occurred was disrupted and further reductions took place. Albumin-globulin ratio reversal was common.

Because of the usual delay in diagnosis and in the hospitalization of patients after the onset of symptoms, treatment was not initiated before the dropping serum albumin level became evident. As a rule, treatment was initiated as soon as possible after the case was accepted for this series.

In the *mild* cases, it was found to be possible not only to halt the decline in albumin level, but actually to raise the level above normal. Probably in most such cases, treatment would not be indicated. In those treated, the patient appeared able to maintain the serum protein levels at or near normal values, and clinical progression of paralysis was arrested or even regressed.

In the *moderate* category, it was possible to stabilize the serum albumin level at whatever level was found present at the onset of therapy. At times it was possible to raise the albumin level to normal, but as a rule it remained slightly subnormal. After therapy was terminated, subnormal albumin levels

persisted for many weeks. There appeared to be little or no intrinsic ability to sustain an artificially elevated albumin level.

In the *severe* class, the maximum benefit obtained from the schedule of therapy used was the temporary stabilization of the dropping serum albumin level. There was little significant tendency shown for it to revert toward normal, and virtually no evidence to indicate that patients could retain the temporary benefit of replacement. When therapy was stopped, the tendency was for the albumin level to resume the decline progressively over an unpredictable period of time (see Charts 1, 2, 3, and 4).

CLINICAL IMPLICATIONS

At the time each case was accepted for this study, each patient was seen by the same staff member* and assigned to one of two well trained physical therapists for complete grading of muscle function. The same technician repeated the muscle grading on the third, seventh, 14th and 21st hospital days. Because of the desire to keep evaluations unbiased, the therapists were not indoctrinated into this program.

The value of plasma therapy is debatable in the mild cases. In those cases the patients appeared to do equally well with or without therapy. The ability to produce serum albumin levels greater than normal is of questionable value. In this report only typical cases were included, and in this discussion no consideration is being given to those patients in whom poliomyelitis progressed from mild to severe. That such progression does occur, however, provides a basis for argument for protein therapy in all cases.

The number of *mild* cases treated was small, for several reasons: (a) the consistency of the favorable response, as indicated by laboratory tests, to the

* John Affeldt, M.D., senior resident, Communicable Disease Unit, Los Angeles County General Hospital.

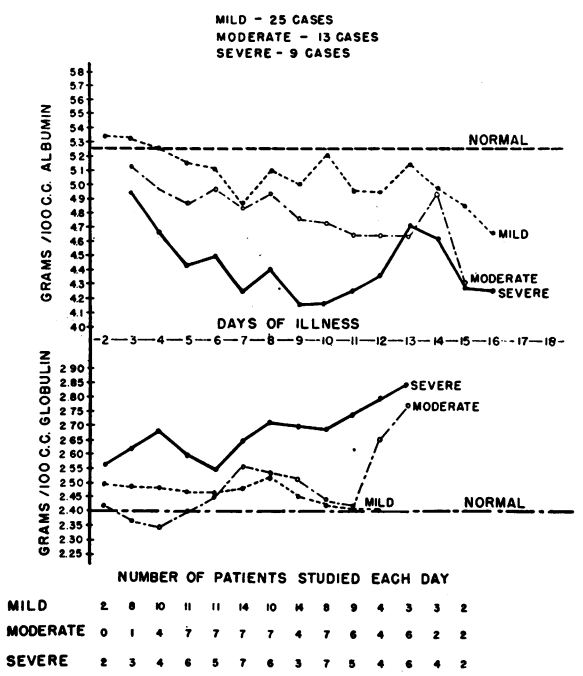

Chart 1.—Serum Protein Levels in Poliomyelitis.

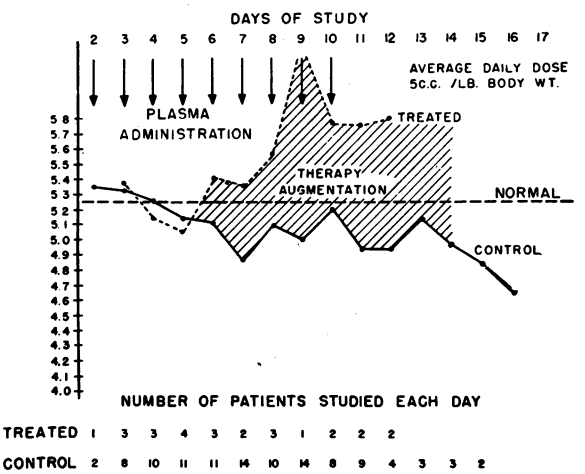

Chart 2.—Serum Albumin Levels in "Mild" Poliomyelitis.

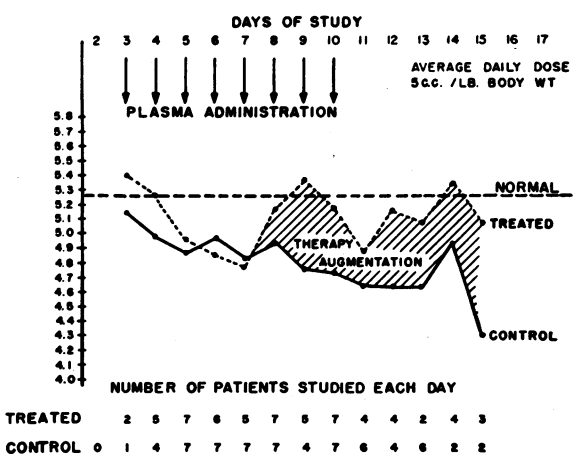

Chart 3.—Serum Albumin Levels in "Moderate" Poliomyelitis.

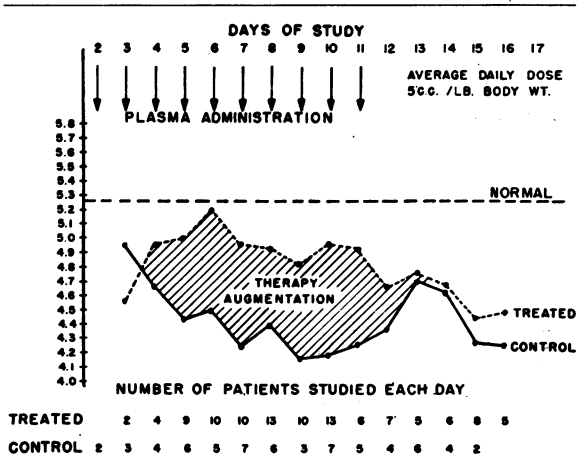

Chart 4.—Serum Albumin Levels in "Severe" Poliomyelitis.

albumin levels; (b) the greater burden of more severely ill patients in *moderate* and *severe* category; and (c) the limitation of supplies of irradiated plasma for this study. Within the small series of treated cases there were no instances of progression observed. On the other hand, in the control series there were repeated instances in which *mild* cases progressed to a more severe category and in which plasma was then given with benefit. These cases, however, were dropped from the series because they did not lend themselves readily to inclusion in this report. When a sufficient number of such instances have been observed and analyzed, future reports will be submitted if data warrant.

In the *moderate* cases, protein therapy produced notable diminution of toxicity. In addition, completed protocols, including the muscle grading charts, warrant the opinion that replacement therapy is of definite value. The dosage of 5 cc. per pound of body weight every 24 hours is probably adequate, but should be carried on longer than five days. It probably should be continued until such time as the laboratory tests reveal a reversion of the serum albumin level to normal over a period of several days.

It is felt that the greatest benefit of protein therapy was to patients in the *severe* category, despite the impression that the dosage used was inadequate and the period of therapy not long enough. Observations made subsequently revealed that larger doses of plasma than those used in this study could not return the serum albumin level to normal. The latter studies were not amplified, but indicated that in the catabolic phases of the illness the replacement therapy was of appreciable benefit: There was a definite diminution of toxemia and an appreciable stabilization, albeit temporary, of the progression of paralysis. There were repeated instances of comatose patients returning to consciousness with plasma therapy, only to relapse after therapy was terminated.

To attain maximum benefit, plasma therapy should be instituted as soon as possible. It was not unusual in the control series, especially in the *severe* category, for relapse to follow temporary clinical stabilization. Because of the critical status of these patients plasma therapy was instituted according to this schedule. Its benefits were easily apparent, but were probably not as efficacious as they might have been if therapy had been instituted earlier. There are no available criteria as yet to prognosticate relapse. The severity of relapse, on the other hand, is well mirrored by falling albumin levels.

DISCUSSION

The authors are aware of the danger of drawing conclusions from a small series of cases. That poliomyelitis is a disease both protean and variable in its manifestation and course is well appreciated, especially since there are no coldly objective criteria of improvement which are not duplicated spontaneously regardless of therapy. Nevertheless, based upon the clinical observation of over 6,000 cases of acute human poliomyelitis in four years, it is felt that an expression of opinion is warranted.

The startling consistency with which depleted serum albumin levels occur in acute human poliomyelitis is a significant contribution to the litera-

TABLE 2.—*Albumin and Globulin Values by Serial Days in Three Patients with Severe Poliomyelitis*

Normal Values: Serum albumin—5.26 grams/100 cc.
Serum globulin—2.31 grams/100 cc.

CASE 1

Days of Illness	Albumin grams/100cc.	Globulin grams/100cc.
13	3.09	3.42
15	2.58	2.95
19	2.71	2.66
23	3.11	3.34
26	3.18	3.41
(Patient relapsed—Condition critical—Plasma given as indicated by symbol Pl.)		
27	3.55	3.61—Pl.
28	3.66	3.75—Pl.
29	....	....—Pl.
30	4.66	3.51—Pl.
31	4.02	3.41
33	3.80	3.00
(Patient unable to maintain levels)		
37	3.80	3.17
40	3.69	3.05
50	4.11	3.00
55	3.73	2.97
60	3.95	2.97
74	4.11	2.93
(Patient lived—Maximum paralysis—Transferred out of hospital in respirator)		

CASE 2

Days of Illness	Albumin grams/100cc.	Globulin grams/100cc.
4	5.04	2.98
5	4.22	2.64
7	4.11	2.12
8	4.38	2.53
10	4.56	2.83
12	4.20	2.76
14	3.66	3.24
(Died on fifteenth day—No treatment)		

CASE 3

Days of Illness	Albumin grams/100cc.	Globulin grams/100cc.
5	4.24	3.24
6	3.98	3.10
7	4.13	3.07
8	4.06	2.63
9	3.18	3.24
(Reversal of ratio)		
10	3.57	3.32
11	4.13	2.44
12	4.15	2.53
13	4.08	2.48
21	4.40	2.85
39	4.20	2.46
59	4.66	2.63
67	4.75	2.32
(Patient lived—No treatment)		

TABLE 3—*Magnitude of Serum Albumin Loss in "Severe" Cases*

Patient	Amount of Serum Albumin Reduction per 100 cc. Serum
1	.5 grams/24 hours
2	.2 grams/24 hours
3	.7 grams/72 hours
4	1.0 grams/72 hours
5	1.1 grams/72 hours
6	.8 grams/72 hours
7	1.0 grams/72 hours
8	2.1 grams/ 6 days
9	1.3 grams/ 4 days
10	1.0 grams/ 2 days
11	1.7 grams/14 days
12	2.3 grams/14 days
13	1.4 grams/ 4 days
14	1.7 grams/10 days

ture and knowledge concerning poliomyelitis, which up to the present time has not been publicized. That this depletion of serum proteins occurs in linear relationship to the severity of paralysis appears to be highly significant. Serum albumin levels of equal magnitude are accepted without dispute as the cause for peripheral edema in other clinical entities. The effects of transfusion of immune bodies in the plasma utilized can be reasonably discounted from the work of Bahlke and co-workers in 1945.[1] The study being presented represents the first known attack therapeutically on a hitherto undescribed physiologic deficiency occurring in human poliomyelitis.

In addition to the data presented here, serum albumin patterns have now been followed in approximately 150 cases (more than 1,600 determinations having been made) and these are consistent in all details with those in the series reported. It remains for others to repeat and substantiate this work in an attempt to crystallize thinking on the benefits which are felt to accrue from the administration of pooled, irradiated human blood plasma in adequate amounts to patients with early poliomyelitis over a sufficiently long period.

It can be stated with assurance that in the *mild* and *moderate* categories not only did results of laboratory tests confirm benefits from administration of plasma, but in no case in the series in which plasma was given early was there clinical progression into a more severe category. Observations within the *severe* group are more controversial, for reasons previously stated. Table 2 presents data that are interpreted as evidence of both laboratory and clinical benefit following treatment as outlined.

TABLE 4.—*Estimate of Clinical Results from "Muscle-Grade" Charts Plus General Clinical Evaluation. (Observations from the Third to the Fourteenth Hospital Days.)*

Category	No. of Cases	Stationary	Progressing	Improved
Mild—not treated	25	17	6	2 (8%)
Treated	4	2	1	1 (25%)
Moderate—not treated	13	8	4	1 (9%)
Treated	9	4	3	1 (23%)
Severe—not treated	9	0	8	1 (10%)
Treated	15	3	8	4 (27%)

It is the primary purpose of this report to describe the acute changes in serum protein levels in human poliomyelitis. These changes have not previously been reported. Secondarily, it is desired to elucidate a rationale for treatment with plasma as well as to report observations in a limited series with such treatment (Tables 2, 3, and 4).

6333 Wilshire Boulevard.

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